A differentiable reformulation for E-optimal design of experiments in nonlinear dynamic biosystems

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Abstract

Informative experiments are highly valuable for estimating parameters in nonlinear dynamic bioprocesses. Techniques for optimal experiment design ensure the systematic design of such informative experiments. The E-criterion which can be used as objective function in optimal experiment design requires the maximization of the smallest eigenvalue of the Fisher information matrix. However, one problem with the minimal eigenvalue function is that it can be nondifferentiable. In addition, no closed form expression exists for the computation of eigenvalues of a matrix larger than a 4 by 4 one. As eigenvalues are normally computed with iterative methods, state-of-the-art optimal control solvers are not able to exploit automatic differentiation to compute the derivatives with respect to the decision variables. In the current paper a reformulation strategy from the field of convex optimization is suggested to circumvent these difficulties. This reformulation requires the inclusion of a matrix inequality constraint involving positive semidefiniteness. In this paper, this positive semidefiniteness constraint is imposed via Sylverster's criterion. As a result the maximization of the minimum eigenvalue function can be formulated in standard optimal control solvers through the addition of nonlinear constraints. The presented methodology is successfully illustrated with a case study from the field of predictive microbiology.

Keywords: Dynamic optimization, Minimum eigenvalue optimization, Nonlinear matrix inequality, Sylvester's criterion, Predictive microbiology

1. Introduction

Dynamic bioprocess models provide valuable insight for the bioprocess industry in view of analysis, control and optimization of bioprocesses. After an accurate model structure has been determined [1], parameter values have to be identified. It is, however, nontrivial to identify param-

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eters in biosystems as these systems often exhibit a strong nonlinear nature. Especially, for cost intensive applications, it can be beneficial to design a dynamic control input in such a way that the experiment yields as much information as possible. In the last decades, optimal experiment design (OED) techniques have gained increasing attention in many bioprocess applications in view of the experimental burden [2, 3, 4, 5, 6, 7, 8, 9]. The first paper to address optimal experiment design for nonlinear dynamic systems is [10]. An overview of the state of the art can be found in [11, 12, 13].

The uncertainty in the parameters is quantified by either (i) the inverse of the Fisher information matrix (FIM) or (ii) another direct approximation technique of the parameter variance-covariance matrix, e.g., the unscented transformation [5, 14, 15, 16]. If these matrices are to be used in an optimization routine in view of designing informative experiments, a specific scalar function of these matrices has to be used as an objective function. In the literature, several functions have been proposed, e.g., minimizing the trace of the inverse of the FIM (A-criterion), maximizing the determinant of the FIM (D-criterion) or maximizing the minimum eigenvalue of the FIM (E-criterion) [11, 15]. Equivalent formulations for the variance-covariance matrix exist and can be found in, e.g., [9]. For some practical applications it can be interesting to combine several design criteria to mitigate the drawbacks of the individual criteria [4, 7, 17, 18].

If the Fisher information matrix approach is followed in optimal experiment design for nonlinear dynamic systems, the parametric sensitivities have to be computed in addition to the original state equations [4, 11, 15]. A first important work that examined the numerical optimization formulation and computation of the variance-covariance matrix for optimal experiment design is [19]. The formulation of optimal experiment design using single shooting [20], multiple shooting [21] or orthogonal collocation [22] has been discussed in depth in these papers. A severe issue is that for nonlinear dynamic systems, the design depends on the current best guess for the parameter value. So, it is important to make the information content of an experiment less dependent on these parameters, i.e., robust optimal experiment design. Two type of approaches exist to tackle this problem. In the first type of approaches an expected value [23, 24, 25] is used which incorporates knowledge on the parameter distribution while in the second approach a worst case max min approach is followed [3, 26]. When optimization routines which exploit gradient based methods are applied, the E-criterion poses numerical challenges. The advantage of gradient based schemes

is that they are fast and can tackle a problem with a large number of decision variables. By construction is the FIM or the variance-covariance matrix, symmetric and positive semidefinite. So, all eigenvalues are nonnegative real numbers but the minimum eigenvalue function can be nondifferentiable. Furthermore, no closed expression exists for eigenvalues of a matrix larger than a 4 by 4 matrix. This means that state-of-the-art optimal control solvers can not exploit automatic differentiation to compute the derivatives with respect to the decision variables as the eigenvalues are normally computed with iterative methods. To overcome these problems a reformulation of the problem can be used [27]. This reformulation involves a constraint requiring positive definiteness. In the current paper these constraints are tackled using Sylvester's criterion [28] in order to enable the use of classic optimal control tools for solving the resulting large scale optimization problems.

The paper is structured as follows. In Section 2, dynamic systems and the mathematical formulation of optimal experiment design is presented. Section 3 discusses the reformulation strategy and how positive semidefiniteness can be enforced using Sylvester's criterion. Section 4 introduces the case study from the field of predictive microbiology. The numerical simulation and optimization results are described in Section 5. Finally, the paper concludes with Section 6.

2. Mathematical formulation

This section discusses first the mathematical description of dynamic systems. In the second part, the formulation of optimal experiment design is presented.

2.1. Dynamic systems

Assume that a system can be described by the following ordinary differential equations in the interval $t \in [0,\ t_\mathrm{f}]$:

$$\dot{x}(t) = f(x(t), p, u(t), t)\ , \tag{1}$$

$$x(0) = x_0\ , \tag{2}$$

$$z(t) = h(x(t))\ . \tag{3}$$

Here, $x(t) \in \mathbb{R}^{n_\mathrm{x}}$ denotes the state vector, $p \in \mathbb{R}^{n_\mathrm{p}}$ a time-invariant parameter vector and $u(t) \in \mathbb{R}^{n_\mathrm{u}}$ is the control input. All these variables enter the right hand side function f in a possibly nonlinear way. The vector x_0 denotes the initial conditions of the system. The function $h(x(t))$ denotes the measurement function of the system which can be nonlinear too, which is usually a

subset of the states $x(t)$. The vector $z(t)$ is the measured output. If there are any path or terminal constraints present, these can be formulated as:

$$0 \geq c_{\mathrm{p}}(x(t), p, u(t), t) \ , \tag{4}$$

$$0 \geq c_{\mathrm{t}}(x(t_{\mathrm{f}}), p, t_{\mathrm{f}}) \ . \tag{5}$$

The measurement error, $\epsilon(t)$ is assumed to be additive to $h(x(t))$ and normally distributed with zero mean, and variance-covariance matrix $Q(t)$. Note that in practice more complex error structures might be needed. A potential approach to transform the measured output to obtain tractable error distributions and to achieve symmetry and constant variance is described in [29].

2.2. Optimal experiment design

In this paper *optimal experiment design for parameter estimation* is considered. The information content in the experiment is quantified by a suitable measure of the Fisher information matrix. This matrix is defined as:

$$F(t_{\mathrm{f}}) = \int_0^{t_{\mathrm{f}}} \frac{\partial x}{\partial p}(t)^{\top} C(t)^{\top} Q(t)^{-1} C(t) \frac{\partial x}{\partial p}(t) dt \ . \tag{6}$$

As the true values for p are not exactly known, the Fisher information matrix is evaluated at the current best guess. The expression $C(t) = \frac{\partial h(x(t))}{\partial x}$ denotes the derivative of the measurement function $h(x(t))$ with respect to the states, x. So, the Fisher information matrix combines information about the variance-covariance matrix of the output error measurements, $Q(t)^{-1}$ and the sensitivities of the states with respect to small variations in the model parameters, $\frac{\partial x}{\partial p}(t)$. These sensitivities are computed as the solutions of the following additional differential equations:

$$\frac{d}{dt}\frac{\partial x}{\partial p}(t) = \frac{\partial f}{\partial x}\frac{\partial x}{\partial p}(t) + \frac{\partial f}{\partial p} \quad \text{with} \quad \frac{\partial x}{\partial p}(0) = \frac{\partial x_0}{\partial p} = 0. \tag{7}$$

An interesting property of the Fisher information matrix is that under the assumption of unbiased estimators and uncorrelated Gaussian noise, the inverse of $F(t_{\mathrm{f}})$ approximates the lower bound of the parameter variance-covariance matrix, i.e, the Cramér-Rao lower bound [15, 30].

In the literature several measures of the Fisher information matrix have been proposed for the design of informative experiments [15], e.g., A-criterion (trace of the inverse of the Fisher information matrix), D-criterion (determinant of the Fisher information matrix). In the current paper the

focus is on the E-criterion, maximizing the smallest eigenvalue of the Fisher information matrix:

$$\max \lambda_{\min}\left(F(t_{\mathrm{f}})\right). \tag{8}$$

This design criterion aims at minimizing the largest parameter error and corresponds to minimizing the length of the largest uncertainty axis of the joint confidence region. The complete dynamic optimization formulation is summarized in:

$$\max_{u(\cdot),x(\cdot),\frac{\partial x}{\partial p}(\cdot),F(\cdot)} \lambda_{\min}(F(t_{\mathrm{f}})) \tag{9}$$

subject to:

$$\begin{aligned}
\frac{dx}{dt}(t) &= f(x(t),p,u(t),t) \quad \text{with} \quad 0 = b_{\mathrm{c}}(x(0)), && (10)\\
z(t) &= h(x(t)), && (11)\\
\frac{d}{dt}\frac{\partial x}{\partial p}(t) &= \frac{\partial f}{\partial x}\frac{\partial x}{\partial p}(t) + \frac{\partial f}{\partial p} \quad \text{with} \quad \frac{\partial x}{\partial p}(0) = 0, && (12)\\
\frac{d}{dt}F(t) &= \frac{\partial x}{\partial p}(t)^{\top} C(t)^{\top} Q(t)^{-1} C(t) \frac{\partial x}{\partial p}(t) \quad \text{with} \quad F(0) = 0, && (13)\\
0 &\geq c_{\mathrm{p}}(x(t),p,u(t),t), && (14)\\
0 &\geq c_{\mathrm{t}}(x(t_{\mathrm{f}}),p,t_{\mathrm{f}})\ . && (15)
\end{aligned}$$

The first two equations describe the actual system dynamics and the predicted output, the following two equations (12) and (13) are the required sensitivity equations and Fisher information matrix equations. Note that the symmetry in $F(t)$ can be exploited. Equations (14) and (15) denote the constraints. The total number of states in the optimal experiment design optimization formulation is $n_{\mathrm{x}} + n_{\mathrm{x}} n_{\mathrm{p}} + n_{\mathrm{p}} \frac{n_{\mathrm{x}}+1}{2}$, where the second term is the number of sensitivity equations and the third term is the number of Fisher information matrix elements.

This type of optimization problems are infinite dimensional, since for every point t in the interval an optimal value has to be found for the control $u(t)$. They can be solved by converting them to a finite dimensional Nonlinear Programming (NLP) problem by means of discretization. Two different approaches can be distinguished. A *sequential direct method* as *Single Shooting* (e.g., [31]) discretizes only the controls while the *simultaneous direct approaches* discretize both states and controls. Within these simultaneous approaches there exist: *Multiple Shooting* (e.g.,

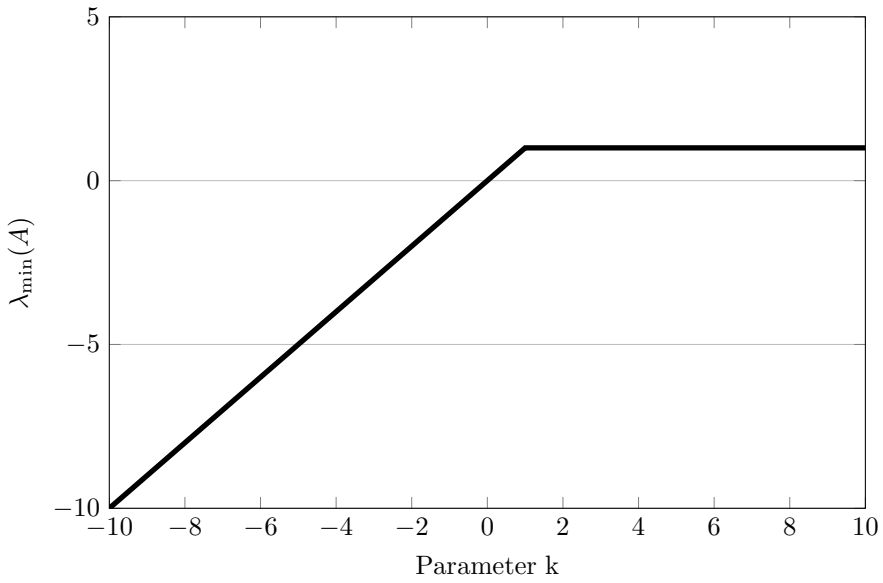


Figure 1: Illustration of the minimum eigenvalue function of the matrix A.

[32]) and *Orthogonal Collocation* (e.g., [33]). Each approach results in a NLP which can be solved by SQP (e.g., [34]) or interior point algorithms (e.g., [35]). However, both type of algorithms require the accurate computation of derivative information, e.g., jacobians of the constraints and the hessian of the objective function.

For the E-criterion, there is, however, a problem with the use of the minimum eigenvalue function in the derivative-based optimization routines. It is possible that the derivative does not exist. Consider the following tutorial example, with a parametrized matrix A:

$$A = \begin{pmatrix} 1 & 0 \\ 0 & k \end{pmatrix} . \tag{16}$$

The evolution of the minimum eigenvalue function as function of the parameter k is depicted in Figure 1. It illustrates that the minimum eigenvalue function of the matrix A is continuous everywhere but that it is not differentiable for $k = 1$. How this problem can be avoided, is discussed in the following section.

3. Reformulation strategy

Using a well-known reformulation strategy from the field of convex optimization, the minimum eigenvalue optimization is reformulated. An additional parameter $\beta \in \mathbb{R}$ is introduced which is to be

maximized. To relate τ with the minimum eigenvalue, a new constraint is added, see Equation (24). The latter equation ensures that τ is bounded by the minimum eigenvalue of the Fisher information matrix. The reformulated problem is described as follows [27]:

$$\max_{u(\cdot),x(\cdot),\frac{\partial x}{\partial p}(\cdot),F(\cdot),\tau} \tau \tag{17}$$

subject to:

$$\begin{aligned}
\frac{dx}{dt}(t) &= f(x(t),p,u(t),t) \quad \text{with} \quad 0 = b_{\mathrm{c}}(x(0)), && (18)\\
z(t) &= h(x(t)), && (19)\\
\frac{d}{dt}\frac{\partial x}{\partial p}(t) &= \frac{\partial f}{\partial x}\frac{\partial x}{\partial p}(t) + \frac{\partial f}{\partial p} \quad \text{with} \quad \frac{\partial x}{\partial p}(0) = 0, && (20)\\
\frac{d}{dt}F(t) &= \frac{\partial x}{\partial p}(t)^{\top} C(t)^{\top} Q(t)^{-1} C(t) \frac{\partial x}{\partial p}(t) \quad \text{with} \quad F(0) = 0, && (21)\\
0 &\geq c_{\mathrm{p}}(x(t),p,u(t),t), && (22)\\
0 &\geq c_{\mathrm{t}}(x(t_{\mathrm{f}}),p,t_{\mathrm{f}}) \ , && (23)\\
F(t_{\mathrm{f}}) - \tau I &\succeq 0 \ . && (24)
\end{aligned}$$

In this dynamic optimization formulation, the last equation, $F(t_{\mathrm{f}}) - \tau I \succeq 0$ denotes that $F(t_{\mathrm{f}}) - \tau I$ is required to be positive semidefinite, i.e., $\forall z \in \mathbb{R}^{n_{\mathrm{p}}} : \ z^{\top}\left(F(t_{\mathrm{f}}) - \tau I\right) z \geq 0$. Equation (24) is a nonlinear matrix inequality as the Fisher information matrix is nonlinearly dependent on the decision variables. This optimization problem can be solved by linearization such that a *linear matrix inequality* is obtained. This formulation allows the use of a semidefinite program solver (e.g., SeDuMi [36]) such that the whole dynamic optimization problem can be solved by sequential semidefinite programming [9]. The problem, however, is that standard optimal control tools do not have dedicated semidefinite program solvers.

Positive semidefiniteness can also be guaranteed using a result from linear algebra. The Sylvester criterion states that a matrix A is positive definite if the determinant of all its principal minors are positive [28] or mathematically expressed:

$$\det(A[(1:i)\times(1:i)]) \quad > \quad 0 \quad \text{with} \quad i = 1,\ldots,n_{\mathrm{p}}. \tag{25}$$

This reformulation allows the nonlinear matrix inequality (24) to be rewritten in n_{p} additional inequality constraints. This leads to the following problem formulation:

$$\max_{u(\cdot),x(\cdot),\frac{\partial x}{\partial p}(\cdot),F(\cdot),\tau} \tau \tag{26}$$

subject to:

$$\begin{aligned}
\frac{dx}{dt}(t) &= f(x(t),p,u(t),t) \quad \text{with} \quad 0 = b_{\mathrm{c}}(x(0)), && (27)\\
\frac{d}{dt}\frac{\partial x}{\partial p}(t) &= \frac{\partial f}{\partial x}\frac{\partial x}{\partial p}(t) + \frac{\partial f}{\partial p} \quad \text{with} \quad \frac{\partial x}{\partial p}(0) = 0, && (28)\\
\frac{d}{dt}F(t) &= \frac{\partial x}{\partial p}(t)^{\top} C(t)^{\top} Q(t)^{-1} C(t) \frac{\partial x}{\partial p}(t) \quad \text{with} \quad F(0) = 0, && (29)\\
0 &\geq c_{\mathrm{p}}(x(t),p,u(t),t), && (30)\\
0 &\geq c_{\mathrm{t}}(x(t_{\mathrm{f}}),p,t_{\mathrm{f}}) \ , && (31)\\
0 &< \det\left((F(t_{\mathrm{f}}) - \tau I)\left[(1:i)\times(1:i)\right]\right) \quad \text{with} \quad i = 1,\ldots,n_{\mathrm{p}}. && (32)
\end{aligned}$$

The above formulation allows the incorporation of the maximization of the minimum eigenvalue in standard optimal control tools. Problems with the nondifferentiability of the objective function are avoided and positive semidefiniteness is ensured through the addition of n_{p} nonlinear constraints.

In order to solve the optimal control problems, the ACADO Toolkit is employed in the current paper [37]. A multiple-shooting setting is adopted. The used integrator is a RK78 with absolute and relative tolerance set to 10^{-6}. The nonlinear program is solved by a SQP routine [34] with tolerances set to 10^{-6}.

Remarks

- In the current paper the information is quantified using the classic Fisher information matrix approach. The reformulation of Equations (26) and (32) can also be used if a different computational method for the approximation of the parameter variance-covariance is used, e.g., the unscented transformation [5, 14]. However, the main advantage of the proposed formulation is that problems with the computation of derivatives are avoided. But this does not exclude the use of the proposed reformulation in optimization algorithm which do not use derivatives, e.g., genetic algorithms, as n_{p} additional nonlinear constraints are easier to evaluate than a nonlinear matrix inequality. However, the discussion and satisfaction of

nonlinear constraints in derivative free stochastic optimization routines is not always trivial.

- The presented approach of the current paper ensures positive definiteness by adding nonlinear constraints. In [9] a formulation has been proposed to guarantee information increase or variance-covariance decrease in a nonlinear matrix inequality way. Also the presence of a matrix inverse (e.g., minimizing trace of the inverse of the Fisher information criterion, i.e., A-criterion) was tackled in [9]. The difference with the presented approach of the current paper is in how the nonlinear matrix inequality is tackled. In the current paper, the matrix inequality is cast in additional nonlinear constraints allowing the use of standard optimal control tools while in [9], the problem is linearized and solved using dedicated semidefinite programming solvers. In general, the presented reformulation of the current paper is also able to tackle the problem formulations of [9].

4. Case study

The case study considered in this paper originates from the field of predictive microbiology. In this field (dynamic) models are constructed to describe the growth, survival and inactivation of micro-organisms in food products. The model concerns the *Cardinal Temperature Model with Inflection point* (CTMI) [38]. This is an adaptation of the Baranyi and Roberts model which describes microbial growth [39]. The dynamic model equations are:

$$\frac{dn(t)}{dt} = \frac{Q(t)}{Q(t)+1}\mu_{\max}(T)[1-\exp(n(t)-n_{\max})] \,, \tag{33}$$

$$\frac{dQ(t)}{dt} = \mu_{\max}(T)Q(t) \,. \tag{34}$$

In this set of equations $n(t)$ [ln(CFU/ml)] expresses the logarithm of the cell density. The factor containing $Q(t)$ is a black-box factor which is introduced to describe the experimentally observed lag phase. $Q(t)$ is assumed to represent a physiological state of the cell population during the lag or adaptation phase. Figure 2a shows the generic evolution of $n(t)$ consisting of three phases, the initial *lag phase* with little growth, the *exponential growth phase* with maximum growth and the final *stationary phase* without growth.

The CTMI model describes the temperature dependency of the maximal growth rate, i.e., $\mu_{\max}(T)$ [38]. The CTMI is illustrated in Figure 2b. If the temperature is below the minimum temperature for growth $T_{\min}$, above the maximum temperature for growth $T_{\max}$, the maximum specific growth

$\mu_{\max}$ is set to 0. Figure 2b presents the presence of one inflection point between $T_{\min}$ and $T_{\opt}$. The mathematical expression of the CTMI is:

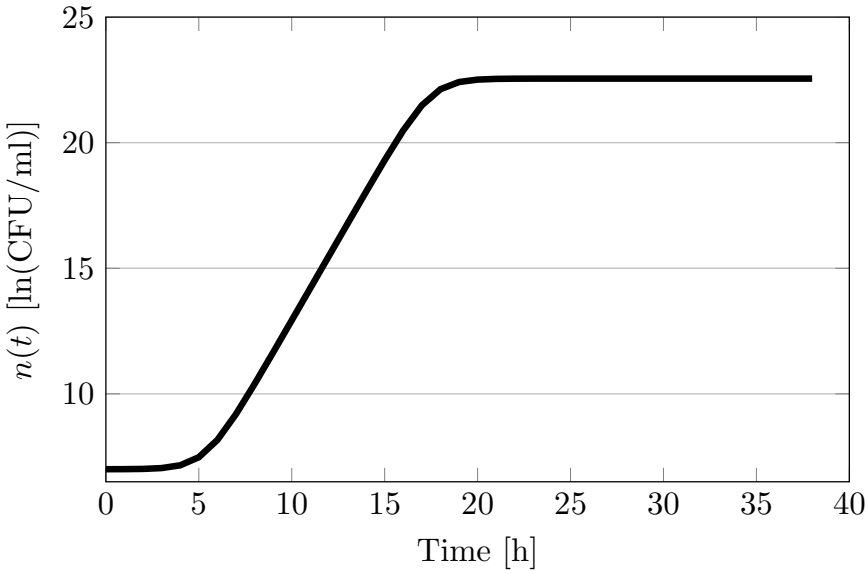
$$\begin{cases} \mu_{\max}(T) = \mu_{\opt}\gamma(T), & \forall T \in [T_{\min}, T_{\max}] \ , \\ \gamma(T) = \frac{(T-T_{\min})^2(T-T_{\max})}{(T_{\opt}-T_{\min})((T_{\opt}-T_{\min})(T-T_{\opt})-(T_{\opt}-T_{\max})(T_{\opt}+T_{\min}-2T))} \ , & \\ \mu_{\max}(T) = 0, & \forall T \notin [T_{\min}, T_{\max}] \ . \end{cases} \tag{35}$$

In this paper microbial growth of *Escherichia coli K12* is investigated. The parameters of the CTMI model which are considered in the optimal experiment design are $p = [T_{\min},\, T_{\max},\, T_{\opt},\, \mu_{\opt}]^\top$ The current best guess for the parameter values for this micro-organism are [40]:

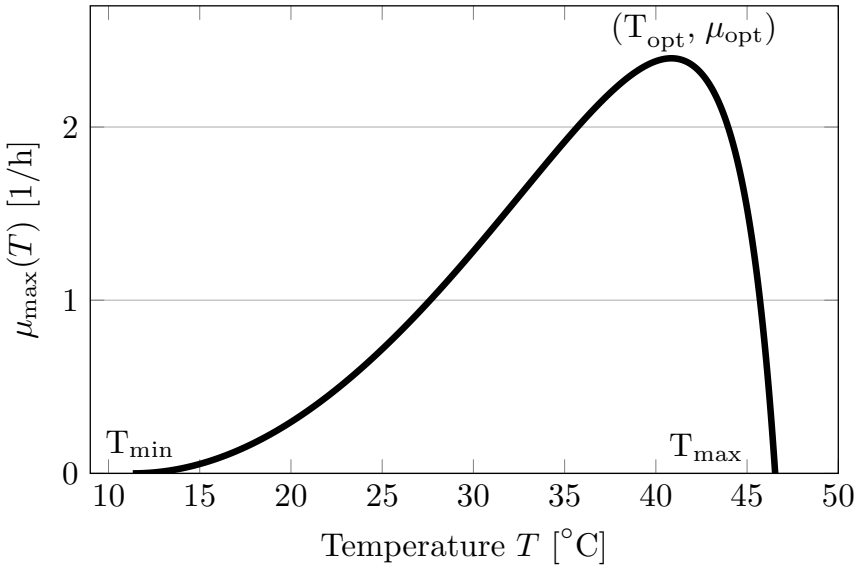
$$T_{\min} = 11.33\,^\circ\mathrm{C}, \qquad T_{\max} = 46.54\,^\circ\mathrm{C},$$
$$T_{\opt} = 40.85\,^\circ\mathrm{C}, \qquad \mu_{\opt} = 2.397\frac{1}{\mathrm{h}} \ .$$

The initial cell density $n(0)$ is in the experiment design assumed to be 7 [ln(CFU/ml)] while the maximum cell density $n_{\max}$ is taken to be 22.55 [ln(CFU/ml)]. The total time of the experiment is set to 38 hours while the control variable in the experiment is the applied temperature profile, $T(t)$. This profile is discretized in 38 piecewise linear intervals. The temperature changes are bounded between -5°C/h and 5°C/h to avoid intermediate lag phases, while the applied temperature is constrained to $T(t) \in [15°\mathrm{C},\, 45°\mathrm{C}]$. The cell density $n(t)$ can be measured and the corresponding measurement error variance is assumed to be equal to 3.2710^{-2} [40].

The extra constraints resulting from the formulation using Sylvester's criterion are illustrated



(a) Graphical representation of the model of Baranyi and Roberts.



(b) Growth rate as a function of temperature, i.e., the CTMI.

Figure 2: Illustration of the Baranyi and Roberts growth model (top) and the CTMI (bottom).

in Equation (36):

$$\text{Constraint 1}: \ \det(F_{11}(t_\mathrm{f}) - \tau) \geq 0, \tag{36a}$$

$$\text{Constraint 2}: \ \det \begin{pmatrix} F_{11}(t_\mathrm{f}) - \tau & F_{12}(t_\mathrm{f}) \\ F_{12}(t_\mathrm{f}) & F_{22}(t_\mathrm{f}) - \tau \end{pmatrix} \geq 0, \tag{36b}$$

$$\text{Constraint 3}: \ \det \begin{pmatrix} F_{11}(t_\mathrm{f}) - \tau & F_{12}(t_\mathrm{f}) & F_{13}(t_\mathrm{f}) \\ F_{12}(t_\mathrm{f}) & F_{22}(t_\mathrm{f}) - \tau & F_{23}(t_\mathrm{f}) \\ F_{13}(t_\mathrm{f}) & F_{23}(t_\mathrm{f}) & F_{33}(t_\mathrm{f}) - \tau \end{pmatrix} \geq 0, \tag{36c}$$

$$\text{Constraint 4}: \ \det \begin{pmatrix} F_{11}(t_\mathrm{f}) - \tau & F_{12}(t_\mathrm{f}) & F_{13}(t_\mathrm{f}) & F_{14}(t_\mathrm{f}) \\ F_{12}(t_\mathrm{f}) & F_{22}(t_\mathrm{f}) - \tau & F_{23}(t_\mathrm{f}) & F_{24}(t_\mathrm{f}) \\ F_{13}(t_\mathrm{f}) & F_{23}(t_\mathrm{f}) & F_{33}(t_\mathrm{f}) - \tau & F_{34}(t_\mathrm{f}) \\ F_{14}(t_\mathrm{f}) & F_{24}(t_\mathrm{f}) & F_{34}(t_\mathrm{f}) & F_{44}(t_\mathrm{f}) - \tau \end{pmatrix} \geq 0 \, . \tag{36d}$$

Remark: A problem with E-optimality is that it is scale dependent, so some standardization is required [41]. In the current paper the Fisher information element is divided by the Fisher information element obtained the D-optimal design [41]. Another possibility is using sensitivities relative to the parameter values as has been employed in, e.g., [42].

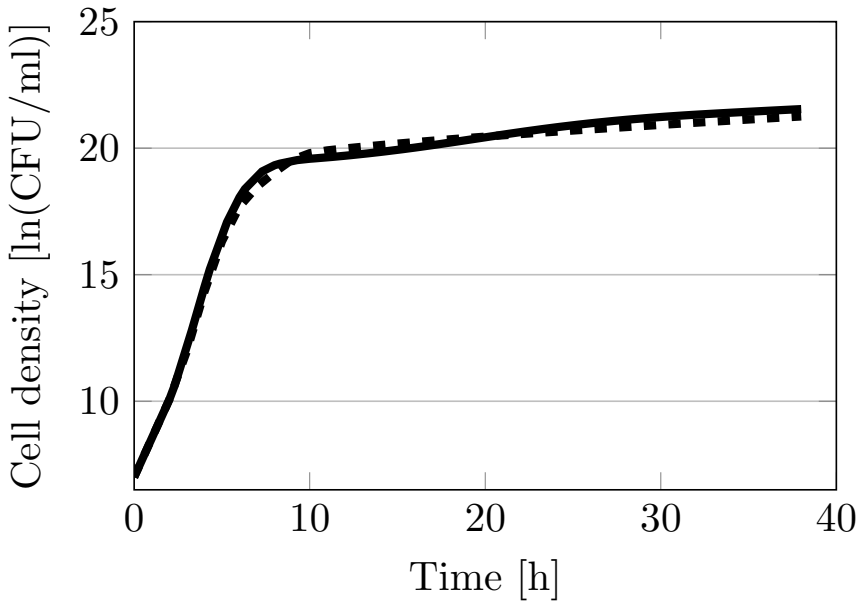
5. Optimization and simulation results

The obtained D- and E-optimal temperature profiles and the corresponding predicted cell densities $n(t)$ are illustrated in Figure 3a and 3b. Both temperature profiles of the D- and E-design in Figure 3b start at the maximum allowed temperature of 45°C and remain at this temperature for 2 hours. After 2 hours both profiles start decreasing for 2 hours with the E-design profile initially at a higher rate than the D-design until 5 hours when the D-design temperature becomes lower than the E-design at that time. Subsequently, the temperature profiles of both designs decrease at the maximum allowed decrease. At 7 hours into the experiment, the D-design results in a small increase in temperature while the E-design remains decreasing but after 8 hours at a slower rate. The E-design reaches the lowest allowed temperature of 15°C after 10 hours but has a gradual increase (up to 17°C at 20 hours into the experiment) and a gradual decrease again to 15°C for the remainder of the experiment. In contrast the D-design reaches the 15°C later and more gradually and remains at this value for the remainder of the experiment.

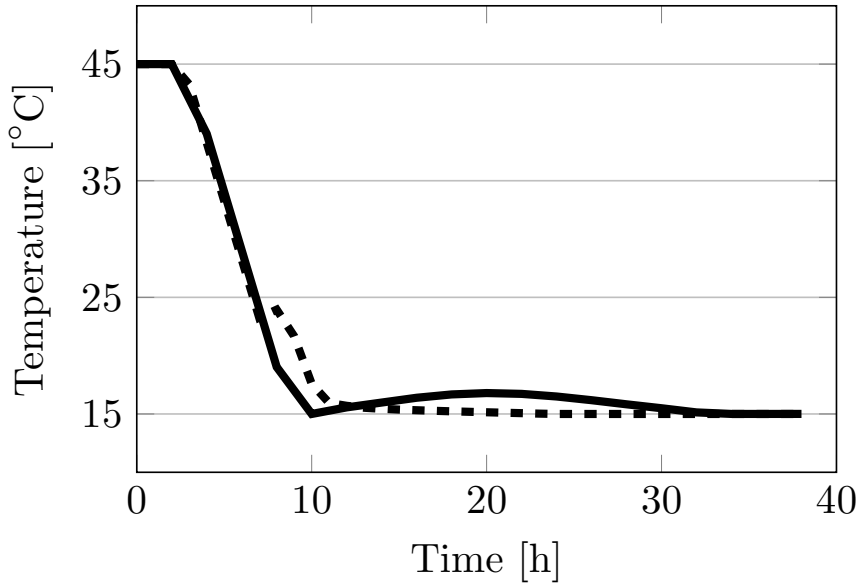
The different effect of the temperature profiles is also visible in the expected cell density profiles of Figure 3a. The first 2 hours there is not much difference between the 2 cell density profiles. As the temperature of the E-design decreases faster and thus closer to T_{opt}, the E-design results in a slightly larger cell density profile up to 8 hours into the experiment. For the effect of the temperature on the growth rate, see also Figure 2b. At 8 hours the temperature profile of the D-design remains longer close to 25°C which results in an increase in the cell density. Due to the fact that the E-design has again a gradual increase up to 17°C, the cell density growth is larger than the corresponding D-design, resulting around 20 hours in a larger cell density again for the E-optimal design.

In order to illustrate the specific effect of the E-design, it is compared to the D-design. More specifically, the following approach has been followed. For both the D-optimal and E-optimal profile, 50 noise realizations are sampled with zero mean and measurement error variance as described in the case study. Measurements are assumed to be taken each hour. This noise is added to the expected state profile based on the current best guess for the parameters. So when performing a parameter estimation, the assumed parameter values are ideally recovered. Hence, for each of these realizations, a parameter estimation procedure is performed. The computed sample mean and variance for the two designs are depicted in Table 1 and 2. As can be seen both designs lead to an acceptable estimation of the initially assumed parameter values. Note that the variance on the least certain parameter, i.e., T_{max} is lower in the E-design than the D-design. This illustrates the fact that the E-criterion focusses on improving the least certain parameter while the D-criterion aims at minimizing the global uncertainty. The price to pay is a slight increase in the variances of T_{min} and T_{opt}.

In practice, the system's true parameter values are not known. So, the experiment has to be informative in the neighborhood of the current estimate of the parameters. In order to investigate whether the designed E-optimal temperature profile is robust in its information content, 8 different parameter cases are considered. Each parameter is slightly perturbed in both positive and negative sense (see Table 3 for an overview). For each of these cases, the previously determined E-optimal temperature profile is used and the corresponding cell density is computed. For each of these 8 cell densities, the parameters thus differ from the ones for which the optimal temperature



(a) Cell density $n(t)$ profile resulting from the E-optimal control profile (full line) and from the D-optimal profile (dashed line).



(b) Optimized control profile with 38 degrees of freedom for the E-optimal design (full line) and the D-optimal design (dashed line).

Figure 3: The obtained temperature (bottom) and predicted cell density profile (top) from the E-design and D-design.

profile has been determined. For each case, 50 noise realizations are sampled and added to the computed cell density profiles. A parameter estimation procedure is performed for a total of 400 in silico experiments.

The resulting mean and variances are presented in Table 4 and 5. From Table 4 it can be inferred that the different mean values accurately approach the assumed parameter values for all different cases. When the variances are investigated, some differences for μ_{opt} are observed. In general, the computed variance for μ_{opt} is one order of magnitude bigger than predicted. For the different temperatures T_{opt} and T_{min}, the variances are of the same order, but for T_{max} there are cases in which the variance increases strongly compared to the original case. Especially, the case where T_{max} and the case where T_{opt} are larger than expected (Case 4 and 6), lead to a significantly larger variance for T_{max} (almost 13 times larger). The parameter T_{max} is observed to be a challenging one to estimate accurately, as in 6 cases, it is larger than in the E-design case. This is also evident from the comparison with the original case (Table 2), where the E-design leads to a decrease in the uncertainty of T_{max} compared to the D-design. So, the E-design increases the accuracy of the least certain parameter but is illustrated to be especially sensitive to its information content if the parameter T_{max} is larger than assumed. Remark also a notable exception with Case 3 (a smaller T_{max}) which leads to a decrease in uncertainty for all parameter values.

Table 1: Empirical mean values of the parameters for in silico parameter estimation with the D- and E-optimal experiment.

Optimal experiments	T_{min}	T_{max}	T_{opt}	μ_{opt}
D-criterion	11.38	46.67	40.84	2.400
E-criterion	11.42	46.71	40.75	2.392

Table 2: Empirical variances of the parameters for in silico parameter estimation with the D- and E-optimal experiment.

Optimal experiments	$s^2_{T_{\text{min}}}$	$s^2_{T_{\text{max}}}$	$s^2_{T_{\text{opt}}}$	$s^2_{\mu_{\text{opt}}}$
D-criterion	0.14	0.56	0.24	0.012
E-criterion	0.16	0.39	0.28	0.0060

Table 3: Parameter combinations used for evaluating the optimal experiment.

Cases	$T_{\min}$	$T_{\max}$	T_{opt}	μ_{opt}
Original	11.33	46.54	40.85	2.397
Case 1	9.00	46.54	40.85	2.397
Case 2	13.00	46.54	40.85	2.397
Case 3	11.33	45.00	40.85	2.397
Case 4	11.33	49.00	40.85	2.397
Case 5	11.33	46.54	39.00	2.397
Case 6	11.33	46.54	42.50	2.397
Case 7	11.33	46.54	40.85	2.300
Case 8	11.33	46.54	40.85	2.500

Table 4: Empirical mean values of the parameters for in silico parameter estimations with the E-optimal temperature profile while the cell density profile is computed from the parameters in Table 3.

Cases	$T_{\min}$	$T_{\max}$	T_{opt}	μ_{opt}
Original	11.42	46.71	40.75	2.392
Case 1	9.075	46.78	40.81	2.394
Case 2	13.05	46.68	40.81	2.401
Case 3	11.37	45.00	40.82	2.404
Case 4	11.42	49.70	40.92	2.393
Case 5	11.30	46.55	39.09	2.411
Case 6	11.41	47.20	42.66	2.414
Case 7	11.36	46.67	40.86	2.312
Case 8	11.33	46.65	40.93	2.511

Table 5: Empirical variances of the parameters for in silico parameter estimations with the E-optimal temperature profile while the cell density profile is computed from the parameters in Table 3.

Cases	$s^2_{T_{\min}}$	$s^2_{T_{\max}}$	$s^2_{T_{\text{opt}}}$	$s^2_{\mu_{\text{opt}}}$
Original	0.16	0.39	0.28	0.0060
Case 1	0.29	0.82	0.42	0.013
Case 2	0.12	0.49	0.38	0.010
Case 3	0.098	0.026	0.33	0.0034
Case 4	0.28	5.53	0.15	0.012
Case 5	0.14	0.37	0.42	0.011
Case 6	0.21	5.46	0.37	0.026
Case 7	0.18	0.83	0.52	0.012
Case 8	0.11	0.73	0.32	0.016

6. Conclusions

In this paper a reformulation strategy for minimum eigenvalue maximization in optimal experiment design has been presented. The minimum eigenvalue maximization corresponds to the E-criterion in optimal experiment design. This function can be nondifferentiable, no expression

exists for matrices larger than a 4 by 4 and the accurate computation of the derivatives with respect to the decision variables can be troublesome. In this paper a reformulation from the field of convex optimization has been employed for designing optimal dynamic experiments. This introduces a matrix inequality requiring positive semidefiniteness. Positive semidefiniteness can be enforced using Sylvester's criterion. This approach allows the maximization of the minimum eigenvalue and ensures positive semidefiniteness in standard optimal control solvers by the addition of several nonlinear constraints. Consequently, accurate derivatives with respect to decision variables can be obtained and numerical problems are avoided. The presented approach has been successfully illustrated with a case study from the field of predictive microbiology.

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References

[1] I. Stamati, F. Logist, E. Van Derlinden, J.-P. Gauchi, J. Van Impe, Optimal experimental design for discriminating between microbial growth models as function of suboptimal temperature, Mathematical Biosciences 250 (2014) 69 – 80.

[2] J. Jacquez, P. Greif, Numerical parameter identifiability and estimability: Integrating identifiability, estimability, and optimal sampling design, Mathematical Biosciences 77 (1985) 201 – 227.

[3] L. Pronzato, E. Walter, Robust experiment design via maximin optimization, Mathematical Biosciences 89 (1988) 161 – 176.

[4] A. C. Atkinson, B. Bogacka, Compound and other optimum designs for systems of nonlinear differential equations arising in chemical kinetics, Chemometrics and Intelligent Laboratory Systems 61 (2002) 17 – 33.

[5] R. Schenkendorf, A. Kremling, M. Mangold, Optimal experimental design with the sigma point method, IET Systems Biology 3 (2009) 10 – 23.

[6] E. Balsa-Canto, A. Alonso, J. Banga, An iterative identification procedure for dynamic modeling of biochemical networks, BMC Systems Biology 4.

[7] D. Telen, F. Logist, E. Vanderlinden, J. Van Impe, Optimal experiment design for dynamic bioprocesses: a multi-objective approach, Chemical Engineering Science 78 (2012) 82–97.

[8] D. Telen, B. Houska, F. Logist, E. Vanderlinden, M. Diehl, J. Van Impe, Optimal experiment design under process noise using Riccati differential equations, Journal of Process Control 23 (2013) 613–629.

[9] D. Telen, F. Logist, R. Quirynen, B. Houska, M. Diehl, J. Van Impe, Optimal experiment design for nonlinear dynamic (bio)chemical systems using sequential semidefinite programming, AIChE Journal 60 (2014) 1728–1739.

[10] D. Espie, S. Macchietto, The optimal design of dynamic experiments, AIChE Journal 35 (1989) 223–229.

[11] G. Franceschini, S. Macchietto, Model-based design of experiments for parameter precision: State of the art, Chemical Engineering Science 63 (2008) 4846–4872.

[12] I. Chou, E. Voit, Recent developments in parameter estimation and structure identification of biochemical and genomic systems, Mathematical Biosciences 219 (2009) 57 – 83.

[13] G. Lillacci, M. Khammash, Parameter estimation and model selection in computational biology, PLoS Computational Biology 6 (2010) e1000696.

[14] T. Heine, M. Kawohl, R. King, Derivative-free optimal experimental design, Chemical Engineering Science 63 (2008) 4873–4880.

[15] E. Walter, L. Pronzato, Identification of Parametric Models from Experimental Data, Springer, Paris, 1997.

[16] J. Vanlier, C. Tiemann, P. Hilbers, N. van Riel, Parameter uncertainty in biochemical models described by ordinary differential equations, Mathematical Biosciences 246 (2013) 305 – 314.

[17] M. Nathanson, G. Saidel, Multiple-objective criteria for optimal experimental design: Application to ferrokinetics, American Journal of Physiology - Regulatory Integrative and Comparative Physiology 17 (3) (1985) R378–R386.

[18] V. Maheshwari, G. Rangaiah, L. Samavedham, Multiobjective framework for model-based design of experiments to improve parameter precision and minimize parameter correlation, Industrial & Engineering Chemistry Research 52 (24) (2013) 8289–8304.

[19] I. Bauer, G. Bock, S. Körkel, J. Schlöder, Numerical methods for optimum experimental design in DAE systems., Journal of Computational and Applied Mathematics 120 (2000) 1–25.

[20] J. Banga, E. Balsa-Canto, Parameter estimation and optimal experimental design, Essays in Biochemistry Volumes 45 (2008) 195–209.

[21] S. Körkel, A. Potschka, G. Bock, S. Sager, A multiple shooting formulation for optimum experimental design, Mathematical Programming(accepted).

[22] M. Hoang, T. Barz, A. Merchan, L. Biegler, H. Arellano-Garcia, Simultaneous solution approach to model-based experimental design, AIChE Journal 59 (2013) 4169–4183.

[23] L. Pronzato, E. Walter, Robust experiment design via stochastic approximation, Mathematical Biosciences 75 (1985) 103–120.

[24] F. Galvanin, M. Barolo, F. Bezzo, S. Macchietto, A backoff strategy for model-based experiment design under parametric uncertainty, AIChE Journal 56 (2010) 2088–2102.

[25] D. Telen, D. Vercammen, F. Logist, J. Van Impe, Robustifying optimal experiment design for nonlinear, dynamic (bio)chemical systems, Computers and Chemical Engineering 71 (2014) 415–425.

[26] S. Körkel, E. Kostina, H. Bock, J. Schlöder, Numerical methods for optimal control problems in design of robust optimal experiments for nonlinear dynamic processes, Optimization Methods and Software Journal 19 (3-4) (2004) 327–338.

[27] L. Vandenberghe, S. Boyd, Semidefinite programming, Society for Industrial and Applied Mathematics Review 38 (1996) 49–95.

[28] D. Wicaksono, W. Marquardt, Reformulation strategies for eigenvalue optimization using Sylvester's criterion and Cholesky decomposition, in: Proceedings of the 23rd European Symposium on Computer Aided Process Engineering (ESCAPE23), 2013, pp. 487–492.

[29] A. Atkinson, Horwitz's rule, transforming both sides and the design of experiments for mechanistic models, Journal of the Royal Statistical Society: Series C (Applied Statistics) 52 (2003) 261–278.

[30] L. Ljung, System Identification: Theory for the User, Prentice Hall, 1999.

[31] V. Vassiliadis, R. Sargent, C. Pantelides, Solution of a class of multistage dynamic optimization problems. 2. Problems with path constraints, Industrial and Engineering Chemistry Research 33 (1994) 2123–2133.

[32] H. Bock, K. Plitt, A multiple shooting algorithm for direct solution of optimal control problems, in: Proceedings of the 9th IFAC world congress, Budapest, Pergamon Press, 1984, pp. 243–247.

[33] L. Biegler, An overview of simultaneous strategies for dynamic optimization, Chemical Engineering and Processing: Process Intensification 46 (2007) 1043–1053.

[34] H. Ferreau, C. Kirches, A. Potschka, H. Bock, M. Diehl, qpOASES: a parametric active-set algorithm for quadratic programming, Mathematical Programming Computation DOI 10.1007/s12532-014-0071-1.

[35] A. Wächter, L. Biegler, On the implementation of a primal-dual interior point filter line search algorithm for large-scale nonlinear programming, Mathematical Programming 106 (1) (2006) 25–57.

[36] J. Sturm, Using SeDuMi 1.02, a MATLAB toolbox for optimization over symmetric cones, Optimization Methods and Software 11–12 (1999) 625–653, version 1.05 available from `http://fewcal.kub.nl/sturm`.

[37] B. Houska, H. Ferreau, M. Diehl, ACADO Toolkit - an open-source framework for automatic control and dynamic optimization, Optimal Control Applications and Methods 32 (2011) 298–312.

[38] L. Rosso, J. Lobry, J. Flandrois, An unexpected correlation between cardinal temperatures of microbial growth highlighted by a new model, Journal of Theoretical Biology 162 (1993) 447–463.

[39] J. Baranyi, T. Roberts, A dynamic approach to predicting bacterial growth in food, Interna-

[40] E. Van Derlinden, K. Bernaerts, J. Van Impe, Simultaneous versus sequential optimal experiment design for the identification of multi-parameter microbial growth kinetics as a function of temperature, Journal of Theoretical Biology 264 (2010) 347–355.

[41] A. Atkinson, K. Chaloner, A. M. Herzberg, J. Juritz, Optimum experimental designs for properties of a compartmental model, Biometrics 49 (1993) 325 – 337.

[42] J. Banga, K. Versyck, J. Van Impe, Computation of optimal identification experiments for nonlinear dynamic process models: a stochastic global optimization approach, Industrial and Engineering Chemistry Research 41 (2002) 2425–2430.